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Occurrence of adverse, often preventable, events in community hospitals involving nephrotoxic drugs or those excreted by the kidney

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Medication errors in patients with reduced creatinine clearance are harmful and costly; however, most studies have been conducted in large academic hospitals. As there are few studies regarding this issue in smaller community hospitals, we conducted a multicenter, retrospective cohort study in six community hospitals (100 to 300 beds) to assess the incidence and severity of adverse drug events (ADEs) in patients with reduced creatinine clearance. A chart review was performed on adult patients hospitalized during a 20-month study period with serum creatinine over 1.5 mg/dl who were exposed to drugs that are nephrotoxic or cleared by the kidney. Among 109,641 patients, 17,614 had reduced creatinine clearance, and in a random sample of 900 of these patients, there were 498 potential ADEs and 90 ADEs. Among these ADEs, 91% were preventable, 51% were serious, 44% were significant, and 4.5% were life threatening. Of the potential ADEs, 54% were serious, 44% were significant, 1.6% were life threatening, and 96.6% were not intercepted. All 82 preventable events could have been intercepted by renal dose checking. Our study shows that ADEs were common in patients with impaired kidney function in community hospitals, and many appear potentially preventable with renal dose checking.

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Medication errors are common in hospitals. Between 44,000 and 98,000 Americans die each year because of medical errors and about 1 million people are injured.[1] The leading cause of medical injury in hospitalized patients in the Harvard Medical Practice Study was the use of drugs, accounting for 19.4% of injuries.[2]

Reduced creatinine clearance is not uncommon in hospitalized patients, and it has important consequences. One review found a rate of 1% on hospital admission, 2–5% during hospitalization, and even higher rates of 4–15% in patients with certain surgical procedures such as cardiopulmonary bypass surgery.[3] A 12-month study controlling for alerts with computerized physician order entry (CPOE) in place found 12% of alerts being associated with renal insufficiency or electrolyte imbalance.[4] Furthermore, reduced creatinine clearance is associated with a 5.5 times higher risk of dying than in patients without reduced creatinine clearance.[5]

Adverse drug events (ADEs) can prolong the length of stay (LOS) and increase costs in patients with reduced creatinine clearance. A study found a mean adjusted increased LOS of 8.2 days and adjusted additional costs of $29,823 in patients with acute renal insufficiency because of amphotericin B therapy.[6] It has been shown that clinical decision support systems can reduce the prolonged LOS in patients with reduced creatinine clearance.[7] In a study including 97,151 medication orders in patients with reduced creatinine clearance, guided medication dosing with clinical decision support systems improved the appropriateness of dose by 13% and appropriateness of frequency by 24%.[7] Furthermore, a randomized, cross-sectional trial in a university hospital intensive care unit-setting in Belgium showed a threefold reduction of medication prescription errors comparing patients with renal insufficiency in a setting with CPOE combined with clinical decision support system with a paper-based setting.[8]

These and other advantages of CPOE systems in improving care led to the formation of the Massachusetts Hospital

CPOE Initiative, which was launched in 2005, with supporting legislation passed in spring 2006.[9] Coordinated by the Massachusetts Technology Collaborative (MTC) and the New England Healthcare Institute in collaboration with the Massachusetts Hospital Association and the Massachusetts Council of Community Hospitals, the initiative has the goal of implementing CPOE in all community hospitals across the state within 4 years.

Relatively few data are available from community hospitals on the frequency of renal insufficiency and the use of nephrotoxic and renally excreted drugs. We therefore assessed the baseline rate of renally impaired patients and their ADE rates in six community hospitals before the introduction of CPOE systems.

RESULTS

Among 109,641 admissions to the six study sites during the observation period, 17,614 (16.1%) were among patients with reduced creatinine clearance (creatinine >1.5 mg/dl). The mean age of patients on admission was 63.2 years (range mean 59.6–72.7 years; Table 1); there was a highly significant difference among sites ($P<0.001$). Of patients overall, 58.1% were women (range 47.2–67.6%, $P<0.001$ among sites) and most patients were white (89.9%, $P<0.001$).

In contrast, patients admitted with reduced creatinine clearance on average were 6.8 years older with a mean age of 75 years (range means 70.8–78.3), with a higher percentage of male patients (57.1%) and a somewhat higher percentage of Caucasian patients (92.2%).

In comparison, patients with reduced creatinine clearance who suffered an ADE were significantly older than the general patient population (mean age 70.3 years, range of means 63.5–75.3, $P<0.001$) but younger than the patient population with reduced creatinine clearance only ($P<0.001$; Table 2). Patients with reduced creatinine clearance and ADE did not show a significant difference regarding gender or race compared with other admissions with reduced creatinine clearance.

During the study period, there were 592 incidents with a rate of 65.8/100 admissions overall (95% confidence interval (CI) 60.6–71.2/100 admissions; Table 3). Most were potential ADEs (84.1%, 55.3/100 admissions) and 15.2% ($n=90$) were ADEs with a rate of 10.0/100 admissions (95% CI 8.1–12.2/100 admissions). There were four medication errors (0.7%) with little potential for harm. The ranges among the study sites varied: the rate of ADEs ranged from 4.0 to 14.0/100 admissions ($P<0.05$) and potential ADEs from 43.3 to 81.3/100 admissions ($P<0.001$). One patient on site 1 had two renal ADEs; all the other patients ($n=88$) had one ADE per patient. Analysis of incidents by type showed that a large proportion of ADEs were judged preventable (91.1 versus 8.9% non-preventable) differing significantly among sites ($P<0.05$). In addition, of 498 potential ADEs 96.6% were not intercepted with a significant difference among sites ($P<0.05$).

Evaluation of incidents by severity showed that most were serious (ADEs 51.1%, potential ADEs 54.4%) or significant (ADEs 44.4%, potential ADEs 44.0%; Table 4). Of ADEs 4.5% were life threatening (0.44/100 admissions, 95% CI 0.14–1.0), whereas 1.6% of potential ADEs were life threatening (0.9/100 admissions, 95% CI 0.41–1.7). None of the incidents was fatal. Almost all of the serious ADEs were preventable (93.5%) and 50.0% of the life-threatening ADEs were preventable. Most of the serious potential ADEs were

Table 1 | Admission characteristics: study population, sites 1–6 (1/1/2005 to 8/31/06)

Characteristic	All patients (n=109,641),%[a]	Site 1,%	Site 2,%	Site 3,%	Site 4,%	Site 5,%	Site 6,%	P-value among sites
Age,[b] mean (range)	63.2 (18–107)	72.7 (18–99)	61.9 (18–99)	59.6 (18–105)	64.6 (18–107)	66.7 (18–103)	59.6 (18–106)	<0.001[c]
18–44	21.5	8.4	27.6	32.1	12.8	14.2	29.9	<0.001[d]
45–54	11.3	7.7	9.4	9.4	14.1	12.5	10.7	
55–64	13.5	9.0	9.9	10.2	19.2	14.4	11.9	
65–74	16.5	16.4	14.2	14.1	21.3	16.7	13.1	
75–84	23.2	32.6	23.5	21.0	23.3	24.7	20.2	
⩾85	14.0	25.9	15.4	13.2	9.3	17.5	14.2	
Gender (%)								
Female	58.1	62.2	63.6	67.6	47.2	58.9	60.3	<0.001[d]
Male	41.9	37.8	36.4	32.4	52.8	41.1	39.7	
Race								
Caucasian	89.9	92.9	93.0	95.0	88.4	86.8	85.9	<0.001[d]
Hispanic	2.6	0.8	0.8	0.4	1.2	6.3	6.9	
Not recorded	2.6	2.4	1.2	0.7	5.7	0.8	1.5	
African American	2.2	2.3	2.2	1.1	1.4	4.3	3.3	
Other	1.5	0.9	1.2	1.8	2.2	0.7	1.1	
Asian	1.1	0.5	1.6	1.0	1.1	1.1	1.3	
Native American	0.1	0.2	0.0	0.0	0.0	0.0	0.0	

[a]For data protection reasons, only percentages are given.
[b]For one patient at site 3 age was not recorded.
[c]One-way analysis of variance.
[d]Fisher's exact test.

Table 2 | Characteristics of admissions with reduced creatinine clearance including an ADE (*n*=89) and comparison with all admissions with reduced creatinine clearance

Characteristic	All sites, *n*=89 (%; *P*-value[c])	Site 1, *n*=17 (%; *P*-value[c])	Site 2, *n*=16 (%; *P*-value[c])	Site 3, *n*=18 (%; *P*-value[c])	Site 4, *n*=21 (%; *P*-value[c])	Site 5, *n*=6 (%; *P*-value[c])	Site 6, *n*=11 (%; *P*-value[c])
Age, mean ((years), s.d.; *P*-value[c])[d]	70.3 (15.2; <0.001[b])	72.3 (12.1; NS[b])	72.6 (16.2; NS[b])	75.3 (13.8; NS[b])	63.5 (14.6;<0.05[b])	65.0 (21.6; NS[b])	71.8 (16.0; NS[b])
18–44	6 (6.7; <0.05[a])	0 (0; 0.05[a])	1 (6.2; NS[a])	1 (5.6; NS[a])	2 (9.5; NS[a])	1 (16.7; NS[a])	1 (9.1; NS[a])
45–54	7 (7.9)	1 (5.9)	1 (6.2)	0	3 (14.3)	2 (33.3)	0
55–64	16 (18.0)	3 (17.6)	3 (18.8)	2 (11.1)	5 (23.8)	0	3 (27.3)
65–74	19 (21.4)	7 (41.2)	1 (6.2)	5 (27.8)	5 (23.8)	0	1 (9.1)
75–84	23 (25.8)	3 (17.6)	5 (31.3)	5 (27.8)	5 (23.8)	2 (33.3)	3 (27.3)
⩾85	18 (20.2)	3 (17.6)	5 (31.3)	5 (27.8)	1 (4.8)	1 (16.7)	3 (27.3)
Gender							
Female	37 (41.6; NS[a])	7 (41.2; NS[a])	6 (37.5; NS[a])	12 (66.7; NS[a])	4 (19.0; NS[a])	2 (33.3; NS[a])	6 (54.4; NS[a])
Male	52 (58.4)	10 (58.8)	10 (62.5)	6 (33.3)	17 (81.0)	4 (66.7)	5 (45.6)
Race							
Caucasian	82 (92.1; NS[a])	17 (100; NS[a])	16 (100; NS[a])	16 (88.9; <0.05[a])	17 (81.0;<0.05[a])	5 (83.3; NS[a])	11 (100; NS[a])
African American	2 (2.2)	0	0	0	1 (4.8)	1 (16.7)	0
Hispanic	3 (3.4)	0	0	0	3 (14.3)	0	0
Other	2 (2.3)	0	0	2 (11.1)	0	0	0

ADE, adverse drug event; NS, not significant.
[a]Fisher's exact test.
[b]*t*-test (for mean age comparison between all patients with reduced creatinine clearance versus patients with reduced creatinine clearance including an ADE.
[c]*P*-values for comparison with all patients with reduced creatinine clearance.
[d]One-way analysis of variance.

Table 3 | Frequency of incidents, by type

	All sites		Comparison across sites[c]	Site 1		Site 2		Site 3		Site 4		Site 5		Site 6	
Incident	*n* (%)	Rate/100 admissions[b]	*P*-value	*n* (%)	Rate/100 admissions	*n* (%)	Rate/100 admissions	*n* (%)	Rate/100 admissions	*n* (%)	Rate/100 admissions	*n* (%)	Rate/100 admissions	*n* (%)	Rate/100 admissions
ADEs	90 (15.2)	10.0 (8.1, 12.2)	<0.05	18 (13.1)	12.0 (7.3, 18.4)	16 (16.2)	10.7 (6.3,16.8)	18 (21.7)	12.0 (7.3,18.4)	21 (22.6)	14.0 (8.8, 20.9)	6 (6.5)	4.0 (1.6, 8.1)	11 (12.6)	7.3 (3.8, 12.6)
Preventable	82 (91.1)	9.1 (7.3, 11.2)	<0.05	15 (83.3)	10.0 (5.8, 15.9)	15 (93.7)	10.0 (5.8,15.9)	18 (100)	12.0 (7.3, 18.4)	20 (95.0)	13.3 (8.3, 20.1)	5 (83.3)	3.3 (1.2, 7.2)	9 (81.8)	6.0 (2.9, 10.8)
Non-preventable	8 (8.9)	0.9 (0.41, 1.65)	NA	3 (16.7)	2.0 (.50, 5.2)	1 (6.3)	0.7 (0.04,2.9)	0	0	1 (5.0)	0.7 (0.04, 2.9)	1 (16.7)	0.7 (0.04, 2.9)	2 (18.2)	1.3 (0.22, 4.1)
Pot. ADEs	498 (84.1)	55.3 (50.6, 60.3)	<0.001	119 (86.9)	79.3 (65.9, 94.5)	83 (83.8)	55.3 (44.3, 68.1)	65 (78.3)	43.3 (33.6, 54.7)	68 (73.1)	45.3 (36.4, 57.0)	87 (93.5)	58.0 (46.7, 71.1)	76 (87.4)	50.7 (40.1, 62.9)
Non-intercepted	481 (96.6)	53.4 (48.8, 58.4)	<0.05	113 (95.0)	75.3 (62.3, 90.0)	80 (96.4)	53.3 (42.5, 65.9)	63 (96.9)	42.0 (32.5, 53.2)	67 (98.5)	44.7 (34.8, 56.2)	84 (96.5)	56.0 (44.9, 68.8)	74 (97.4)	49.3 (39.9, 61.4)
Intercepted	17 (3.4)	1.9 (1.1, 2.9)	NS	6 (5.0)	4.0 (1.6,8.1)	3 (3.6)	2.0 (0.50,5.2)	2 (3.1)	1.3 (0.22, 4.1)	1 (1.5)	0.7 (0.04, 2.9)	3 (3.5)	2.0 (0.50, 5.2)	2 (2.6)	1.3 (0.22, 4.1)
Medication errors[a]	4 (0.7)	0.4 (0.14,1.0)	NA	0	0	0	0	0	0	4 (4.3)	2.7 (0.83, 6.2)	0	0	0	0
Total	592 (100)	65.8 (60.6, 71.2)		137 (100)	91.3 (76.9, 107.5)	99 (100)	66.0 (53.8, 79.9)	83 (100)	55.3 (44.3, 68.1)	93 (100)	62.0 (50.2, 75.5)	93 (100)	62.0 (50.2,75.5)	87 (100)	58.0 (46.7, 71.1)

NA, not applicable; NS, not significant; Pot., potential.
[a]Medication errors with little potential for harm.
[b]Admissions with reduced creatinine clearance.
[c]χ^2-test for equal rates across sites.

not intercepted (97.8%) and all life-threatening potential ADEs were non-intercepted. All of the 82 preventable ADEs could have been prevented by renal dose checking.

Of potential ADEs, nearly all (99.8%; 497/498) could have been prevented by CPOE systems with decision support: 495 (99.4%) by renal dose checking, 1 (0.2%) by drug dose suggestion, 1 (0.2%) by cumulative dose check; 1 potential ADE (0.2%) was not preventable by CPOE. Analysis of the preventable ADEs ($n=82$) showed that most were caused by the use of too high a dose of a renally cleared or nephrotoxic drug in the presence of rising creatinine. Most ADEs were worsened renal function, with 89% including a rising creatinine. In 3.7%, bradycardia/hypotension and hypoglycemia occurred, with oversedation in 2.4% and nausea in 1.2%. The type of error was almost exclusively the choice of a wrong dose in 86.6% or the wrong frequency in 12.2%.

Kappa statistics for inter-rater reliability showed an 88.4% agreement for ADE versus no ADE ($\kappa=0.46$, 95% CI 0.36–0.56), 88.6% agreement for ADE versus potential ADE or exclusion ($\kappa=0.48$, 95% CI 0.37–0.58), and 95.1% agreement for preventable versus not preventable ($\kappa=0.64$, 95% CI 0.18–1.00).

Table 4 | Incidents, by preventability and severity

Incident	All sites			
	ADEs			
	n (%)	Rate/100 admissions (95% CI)	Non-preventable, *n* (%)	Preventable, *n* (%)
Significant	40 (44.4)	4.4 (3.2–6.0)	3 (7.5)	37 (92.5)
Serious	46 (51.1)	5.1 (3.8–6.7)	3 (6.5)	43 (93.5)
Life threatening	4 (4.5)	0.44 (0.14–1.0)	2 (50.0)	2 (50.0)
Total	90 (100.0)	10.0 (8.1–12.2)	8 (8.9)	82 (91.1)
	Potential ADEs			
			Non-intercepted, *n* (%)	Intercepted, *n* (%)
Significant	219 (44.0)	24.4 (21.4–27.8)	208 (95.0)	11 (5.0)
Serious	271 (54.4)	30.1 (26.7–33.8)	265 (97.8)	6 (2.2)
Life threatening	8 (1.6)	0.9 (0.41–1.7)	8 (100)	0
Total	498 (100.0)	55.3 (50.6–60.3)	481 (96.6)	17 (3.4)

ADE, adverse drug event.

Table 5 | Drug classes involved in ADEs

Drug class	Number of drugs involved in ADEs, preventable Total, *n* (%)	Number of drugs involved in ADEs, non-preventable Total, *n* (%)	Drugs
Antibiotics	100 (37.0)	6 (42.9)	Ampicillin (and sulbactam), cefaclor, cefazolin, cefotaxime, ceftazidime, cefuroxime axetil, ciprofloxacin, erythromycine, gatifloxacin, gentamycin sulfate, imipenem, levofloxacin, metronidazole, penicillin G, piperacillin and tazobactam sodium, trimethoprim-sulfomethoxazole, tobramycin sulfate, vancomycin.
Analgesics	85 (31.5)	3 (21.4)	Acetaminophen, codeine and acetaminophen, hydrocodone, ketorolac, meperidine, morphine (sulfate), oxycodone and acetaminophen, propoxyphene and acetylic salicylic acid and acetaminophen.
Non-narcotic, non-NSAID*	45 (53.0)	1 (33.3)	
		1 (33.3)	
Narcotic	39 (45.9)		
NSAID	1 (1.1)	1 (33.3)	
Cardiovascular	44 (16.3)	4 (28.6)	Atenolol, bumetanide, captopril, digoxin, enalapril, hydralazine, hydrochlorothiazide, lisinopril, sotalol, spironolactone, quinapril.
ACE inhibitors	24 (54.5)	2 (50.0)	
Antiarrhythmics	11 (25.0)	—	
Diuretics	6 (13.6)	1 (25.0)	
β-Blockers	3 (6.8)	1 (25.0)	
Diabetes	12 (4.4)	—	Glipizide, glyburide, metformin.
Oral antidiabetics	12 (100)	—	
Antifungal agents	11 (4.1)	—	Fluconazole
Neurotropic drugs	2 (0.7)	—	Lithium, midazolam
Sedatives	1 (50.0)	—	
Antipsychotics	1 (50.0)	—	
Other drugs	16 (5.9)	1 (7.1)	Allopurinol, colchicine, famotidine, ranitidine, sucralfate.
Gastrointestinal	9 (56.2)	—	
Anti-gout	5 (31.3)	—	
Unknown	2 (12.5)	1 (100)	
Total no. of drugs	270 (100)	14 (100)	

ACE inhibitors, angiotensin-converting enzyme inhibitors; ADE, adverse drug event; NSAID, non-steroidal anti-inflammatory drugs.

Antibiotics ranked first regarding drugs involved in ADEs: 37% of preventable and 42.9% of non-preventable ADEs were caused by antibiotics; most classes of antibiotics such as penicillins, aminoglycosides, cephalosporins, and macrolides were affected (Table 5). Analgesics ranked second causing 31.5% of preventable and 21.4% of non-preventable ADEs. In this class, acetaminophen alone or as a compound drug and opiates with derivates was most frequent. Cardiovascular drugs ranked third causing 16.3% of preventable and 28.6% of non-preventable ADEs. Angiotensin-converting enzyme - inhibitors, antiarrhythmics, and diuretics were the most frequent drugs in this category. Antifungal, oral antidiabetic, and neurotropic agents caused each $<5\%$ of ADEs.

The diagnosis-related group-weighted LOS of all patients at the study centers was higher than that of the national average ($+0.20$ days; $P \leqslant 0.001$).[10] Patients admitted with

Table 6 | Length of stay: patients with renal insufficiency and ADEs in comparison with other admissions

	Total no. of admissions	Attributable length of stay, mean (s.d.)	Overall, range	Range among 6 sites[b]	Difference (*P*-value[c])
A. DRG-weighted national average LOS	(109,641[a])	4.60 (3.09)	0–42.9	4.0–5.1	Reference
B. All admissions study centers	109,641	4.80 (5.35)	0–276	3.9–6.0	+0.20[d]
C. Admissions with reduced creatinine clearance	17,614	7.08 (7.25)	0–115	5.8–7.8	To A: +2.48[d] B: +2.28[d]
D. Admissions with reduced creatinine clearance and ADE	90	12.29 (9.85)	1–46	6.9–15.0	To A: +7.69[d] B: +7.49[d] C: +5.21[d]

ADE, adverse drug event; DRG, diagnosis-related group; LOS, length of stay.
[a]DRG adjusted to group B; DRG-weighted LOS could be obtained for 99.43% of patients.
[b]Range of site average.
[c]*t*-test.
[d]$P < 0.001$.

reduced creatinine clearance showed an additional average LOS of +2.28 days compared with other patients at the study sites (Table 6; groups C versus B, $P = < 0.001$). Patients admitted with reduced creatinine clearance who suffered an ADE stayed on average additional 5.21 days compared with the patients with reduced creatinine clearance alone (groups D versus C, $P = < 0.001$) and +7.49 days compared with all the admissions during the study period at the six study centers (groups D versus B, $P = < 0.001$).

DISCUSSION

We found that one in 10 patients with baseline renal insufficiency suffered an ADE in this community hospital population. For every ADE, there were about five potential ADEs. Of all renal ADEs, nine of 10 were considered preventable. Half of the life-threatening ADEs were considered preventable. The prevention strategy with the greatest potential benefit was renal dose checking. ADEs were associated with a substantial prolongation of LOS.

Overall, ADE rates including ADEs of all types, not just renal ADEs, in one study were 6.5/100 admissions in an academic tertiary referral hospital in the same region.[11] By contrast, in this study there were about 1.5 renal ADEs per 100 admissions. In another study, in this population reported elsewhere, we found an ADE rate of 15.0/100 admissions (Hug BL LS1 *et al.*, unpublished data). Kilbridge *et al.*[12] have reported previously that ADEs differ somewhat regarding frequency and quality between community hospitals and tertiary referral hospitals. However, relatively speaking, few data are available assessing the frequency of ADEs in community hospitals and more evaluations would be helpful.

In addition to the overall high preventability of ADEs, all the preventable ADEs might have been potentially preventable by renal dose checking, a measure that can relatively easily be introduced into existing CPOE systems. Chertow *et al.* found that an inexpensive decision support system added to CPOE significantly improved drug dosing in patients with renal insufficiency, although there was still substantial room for improvement.[13] The same study showed a reduction of the LOS of 0.5 days for patients with renal insufficiency. In another study of psychotropic medication use in a geriatric population, when clinical decision support was delivered, agreement with recommended dosing guidelines improved by 34% and the fall rate fell significantly.[14] Rind *et al.*[15] showed that using physician alerts in patients with rising serum creatinine levels invoked a faster physician reaction regarding drug choice and dose adaptation, reduced the risk of serious renal impairment by 55%, preserved renal function and was well accepted by the physicians involved. Furthermore, Nash *et al.*[16] found that implementing an automated system to complement an existing CPOE system made the baseline rate of excessive dosing in patients with renal impairment decrease from 23.6 to 17.3%.

In this study, antibiotics, analgesics, and cardiovascular drugs were most frequently involved in causing ADEs. The list of drugs potentially causing acute renal insufficiency is long: affecting renal hemodynamics (e.g., non-steroidal anti-inflammatory drugs, nonsteroidal anti-inflammatory drugs), direct tubular toxicity (e.g., aminoglycosides), intratubular obstruction-like sulfonamides and certain human immunodeficiency virus drugs (e.g., indinavir), as well as allergic interstitial nephritis (e.g., penicillins, cephalosporins, diuretics).[12,13] Classen *et al.*[17] found a similar array of culprit drugs, namely, analgesics (morphine and derivates, acetaminophen), antiarrhythmic drugs (digoxin), antibiotics (imipenem, cefazolin, vancomycin), as well as meperidine and warfarin. Gandhi *et al.*[18] found in their analysis of 181 ADEs in an ambulatory setting that 10% were caused by selective serotonin reuptake-inhibitors, 9% by β-blockers, 8% each by angiotensin-converting enzyme inhibitors and nonsteroidal anti-inflammatory drugs.

Adverse drug events in patients with impaired renal clearance are dangerous and prolong the LOS. Our results showed a highly significant excess LOS of patients with reduced creatinine clearance (+2.28 days) and additionally through suffering an ADE (+5.21 days) compared with the average of all patients. Although these numbers may seem high, a study on cost and nephrotoxicity of amphotericin B showed very similar results: Bates *et al.*[6] found that in the case of acute renal insufficiency in patients exposed to amphotericin B the mean adjusted increase in LOS was 8.2 days. In patients with reduced creatinine clearance and ADE LOS is higher compared with patients with ADEs in general. Overall, Classen *et al.* found an adjusted additional increase in LOS of 1.91 days in patients with ADEs,[16] while Bates *et al.* showed an increase of LOS of 2.2 days and for preventable ADEs the increase of LOS was 4.6 days.[19]

Our study has several limitations. Patient populations might show differences between hospitals on the basis of age and case mix. We therefore averaged results among the six community hospitals. Furthermore, patients were mainly Caucasian and results in hospitals with more minority patients might have different results. Although random sampling with trigger tools is a widely acknowledged way of measuring safety and specifically ADE incidence in hospitals on wards as well as intensive care units,[20] it may not represent all ADEs occurring at a test site. To our knowledge, although, it is to date the best way to balance cost, time-consumption, and effectiveness detecting ADEs in institutions without any CPOE or electronic medical records in place, and is especially well suited to assess renal ADEs because of the accessibility of creatinine. As in many cases we did not have the complete renal history at our disposal, it was not possible to discern between acute, chronic, or acute on chronic renal failure. In addition, most of the ADEs were increases in creatinine, and we could not be certain that they were related to the nephrotoxic medications being given in any specific instance, so that other factors may have caused some of the elevations in creatinine. Assessment of presence of ADEs was based on reviewer judgment, and agreement was not complete. However, our inter-rater reliability was comparable with earlier studies.[11] In some of the study sites CPOE systems were about to be implemented, which might have caused a higher awareness of the medical staff regarding drug safety issues compared with other sites. The study sites are located in one state in the northeast; the results may therefore not be generalizable to other regions.

In summary, we found that ADEs were common in patients with reduced creatinine clearance and that they prolonged hospital stays. Most are likely preventable with renal dose checks combining laboratory values with pharmacy databases. Although the rates of renally related ADEs varied somewhat by hospital, all would benefit by introducing this decision support.

MATERIALS AND METHODS

Study design

We conducted a retrospective cohort study with chart review of admissions within the period from 1 January 2005 until 31 August 2006. The Brigham and Women's Hospital Institutional Review Board, as well as the local review boards of all study sites approved the investigation.

Study centers

The study centers were six community hospitals in Massachusetts with 100 to 300 beds; three had house staff, and three did not.

Patient population

All hospitalized patients from the six study sites were included during the study period accounting for a total of 109,641 admissions. Patients were defined as having reduced creatinine clearance at baseline be it acute or chronic if they had a creatinine of 1.5 mg/dl or higher. The study included 17,614 (16.1%) admissions of patients with acute or chronic reduced creatinine clearance.

Case finding and definitions. All patients with a creatinine over 1.5 mg/dl measured on first occurrence during the study period and exposed to potentially nephrotoxic or renally cleared drugs were identified from the population of all patients hospitalized during the observation period. Duration of reduced creatinine clearance was not known; therefore chronic, acute, and acute on chronic renal failure were all likely present in the study population, although we suspect chronic kidney disease predominated. A random number generator was used to select 150 admissions from each of the six study sites.

To assess the level of renal function, trained study nurses obtained body weight and height measurements from the charts, and renal clearance was computed according to Cockroft–Gault ((140 – age) $\times$ weight/serum creatinine $\times$ 72, correction factor of 0.85 for women).[21] Subsequently, patients were stratified into three levels of renal insufficiency: level 1 with creatinine clearance of $<$15 ml/min, level 2 with 15–50 ml/min, and level 3 with 50–80 ml/min. Creatinine clearance above 80 ml/min was considered normal. The study then followed the dosage guidelines for all three levels of renal insufficiency as developed previously at the Brigham and Women's Hospital, Boston.[7]

Trained study nurses identified incidents that suggested a medication error or ADE using the Institute of Healthcare Improvement trigger tool as described by Rozich *et al.*[22,23] Each incident was independently reviewed by two physicians and classified according to type, severity, and preventability as published elsewhere.[11,24,25] In brief, an incident was first classified as to whether or not it was a medication error, a potential ADE or an ADE. An incident was defined as any irregularity in the process of medication use, a general term before classification into medication error, ADE, or neither of both.[24] A medication error was defined as an error in the process of ordering or delivering a medication, regardless of whether an injury occurred or not.[25] An ADE was defined as an injury related to a drug; a potential ADE was defined as medication error with the potential for injury, but in which no injury occurred.[25] Second, incidents were reviewed for severity as significant (e.g., rash), severe (e.g., gastrointestinal bleed), life threatening (e.g., transferal to intensive care unit), or fatal.[26] To stratify the extent of reduced creatinine clearance, we used the Bonney Criteria: an increase $<$10% of patient creatinine was considered a potential ADE, an increase of 10–100% a significant ADE and more than 2$\times$ baseline creatinine a serious ADE.[27] Increases in creatinine were considered ADEs only for drugs with nephrotoxicity, and not for renally excreted drugs. Third, preventability was classified as probably preventable, definitely preventable, probably not preventable and definitely not preventable.[28] Preventability was consequently collapsed into preventable (probably and definitely preventable) or not preventable (probably and definitely not preventable). In case of disagreement regarding type, severity, or preventability of the incident, the physician reviewers met for reconciliation. If consensus could not be reached a third party reviewer evaluated the incident. Kappa statistics for inter-rater reliability were then computed. Judgment of potential preventability by CPOE systems was made implicitly, but these judgments were grounded by earlier studies that documented an error reduction when CPOE was implemented, for example, regarding dose, frequency, route of application, drug substitution, allergy, avoidable delay, and drug–drug interactions.[29]

Main outcome measures

The main outcome measures were incidence, type, severity, and preventability of ADEs before introduction of CPOE systems and

the estimation of potential benefit in diagnosis-related group-weighted LOS compared with former studies.[19]

Average LOS

Average LOS per patient was computed. These were weighted by diagnosis-related group for all admitted patients. Patients with reduced creatinine clearance and ADEs were compared with the national average and those with reduced creatinine clearance who did not suffer an ADE.

Data analysis

All categorical variables are reported as percentages in summary statistics. For comparison of categorical variables, we used χ^2 and Fisher's exact test, for comparison of means the *t*-test and the analysis of variance procedure. As threshold of statistical significance we used an $\alpha = 0.05$. For statistical analysis we used the SAS 9.1 package (SAS Institute, Cary, NC).

DISCLOSURE

This study was funded by the Massachusetts Technology Collaborative, which is not responsible for the contents of the paper. Dr Bates is a co-inventor on patent no. 6029138 held by Brigham and Women's Hospital on the use of decision support software for medical management, licensed to the Medicalis Corporation. He holds a minority equity position in the privately held company Medicalis, which develops web-based decision support for radiology test ordering, and serves as a consultant to Medicalis. He is a consultant for Cardinal Health, which makes intravenous drug delivery systems. Dr Hug has received financial funding from the Freie Akademische Gesellschaft, the Walter and Margarethe Lichtenstein Fund, and the University Hospital in Basel, Switzerland.

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